
# Zollinger-Ellison Syndrome With Pancreatic Islet Cell Hyperplasia

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In 1955 Zollinger and Ellison[15] described two cases in which primary jejunal ulcers were associated with pronounced gastric hypersecretion, hyperacidity and non-insulin producing islet cell tumors of the pancreas and they postulated a definable clinical entity made up of this complex of conditions. Soon afterward Eiseman,[2] discussing a later communication, suggested that this clinical entity be called the Zollinger-Ellison Syndrome.

It was early proposed by Zollinger and McPherson[16] that hyperplasia of the islets in the pancreas might be implicated in the severe ulcer diathesis requiring total gastrectomy, and a case in point was presented. The condition was likened to that in the parathyroid gland in which hyperplasia of the cells results in clinical and laboratory features identical to those produced by a true adenoma. Summerskill[7] studied a similar case. The ulcerogenic potential of hypertrophy and hyperplasia of the islets was considered by Zollinger and Craig.[12] They noted hyperplasia of the islets was of little diagnostic significance because it occurs in association with many different conditions.

In the case herein presented, many of the features of the Zollinger-Ellison syndrome were present, but no islet cell tumor could be found. The pancreas showed islet cell hyperplasia.

Submitted March 16, 1964.

## Report of a Case

A 34-year-old Negro truck driver was admitted to hospital February 15, 1963, with chief complaint of intermittent upper abdominal pain of eight months' duration. He had been in good health before that time. The pain was burning in nature and radiated to the midback from the epigastric area. Ingestion of food, milk and antacids partially relieved it. It was often associated with nausea and vomiting but not with hematemesis or melena.

Five months before admission, he had been put in hospital elsewhere and after x-ray examination a diagnosis of multiple duodenal ulcers was made. At that time, serum calcium was 9.5 mg per 100 ml and serum phosphorus 3.7 mg per 100 ml. Results of serologic tests for syphilis were negative. A 12-hour gastric specimen measured 1180 ml with a total acidity of seven clinical units and free hydrochloric acid zero clinical units. There was a possibility that the patient had taken antacids, accounting for the low acidity. He was discharged asymptomatic after conservative treatment.

Three weeks before the present admission, abdominal pain returned and he noted considerable diarrhea during that time.

He drank a half pint of whisky per day and smoked about ten cigarettes. The family history was not remarkable. On physical examination the only abnormality noted was mild tenderness in the epigastrium and the right upper quadrant of the abdomen.

An upper gastrointestinal tract roentgenographic examination on February 17, 1963, showed a large active duodenal ulcer with disturbances in the motility pattern of the small bowel. A second gastrointestinal series on March 15, 1963, showed a duodenal ulcer and abnormal small bowel pattern and motility. Studies of the blood showed the hemoglobin was 15.1 gm per 100 ml, leukocytes 9,900 per cu mm, a serologic test positive for syphilis, serum calcium 9.7 mg per 100 ml, serum phosphorus 5.2 mg per 100 ml, serum potassium 4.5 mEq per liter, amylase 102 units, and a normal glucose tolerance curve. The results of 12-hour gastric anal-

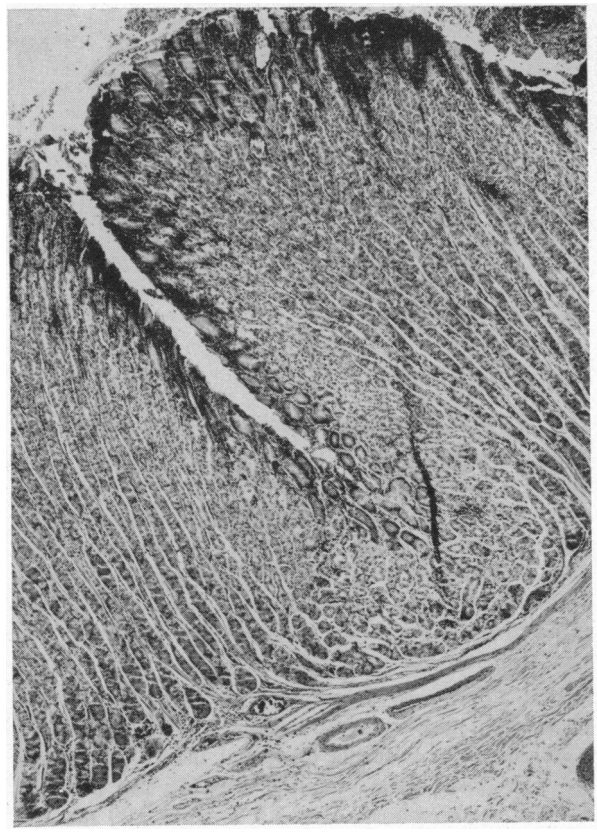

**Figure 1.—Gastric mucosa with increase in parietal cells (× 40).**

ysis on several occasions are listed in Table 1. The xylose absorption, from a 260 ml five-hour specimen of urine was 7.8 gm (normal 5.3 to 7.7 gm).

The patient was admitted to the medical service, where a clinical diagnosis of Zollinger-Ellison syndrome was made in light of the presence of duodenal ulcers, large total 12-hour gastric volumes, a large amount of free hydrochloric acid formed in the stomach, diarrhea and the abnormalities shown in the small bowel by x-ray films. At abdominal laparotomy April 25 an ulcer was seen in the first portion of the duodenum. Two suspicious-looking lymph nodes at the head of the pancreas were normal on frozen section. Two nodules, each measuring approximately 0.5 centimeter, were located in the tail of the pancreas. The tail of the pancreas was resected with splenectomy; however, no diagnosis of neoplasm could be made from frozen section. Vagotomy and high subtotal gastric resection and gastrojejunostomy were carried out. The duodenal and proximal jejunal lumina were visualized and palpated but no evidence of tumor was observed. Postoperatively, the acidity of the gastric aspirate was low (Table 1). The patient was discharged May 14, 1963.

*Pathologic examination.* The sections of the pancreas showed hyperplasia of islet cells with an increase in the total volume of islet cells. An increase in the parietal cells was noted throughout the gastric mucosa (Figure 1).

**TABLE 1.—*Results of Gastric Analysis on 12-Hour Overnight Gastric Aspirations***

| Date | Total Volume | (Units per 100 ml of Gastric Juice) Total Acid | Free Acid |
|---|---|---|---|
| ‡10-18-62 | 1,180 | 7 | 0 |
| 3-19-63 | 2,600 | 120 | 103 |
| 3-26-63 | 4,550 | 105 | 50 |
| *4-30-63 | 820 | 37 | 0 |
| *5-9-63 | 145 | 5 | 0 |
| *6-5-63 | 1,100 | 14 | 0 |

‡Admission elsewhere.
*Postoperative.

**TABLE 2.—*Results of Hollander Test—6/12/63***

| Minutes | Blood Glucose (mg %) | Free Acid (Units HCl/100 cc Gastric Juice) | Total Acid (Units HCl/100 cc Gastric Juice) |
|---|---|---|---|
| 15 | .... | 0 | 10 |
| 30 | 74 | 0 | 10 |
| 45 | .... | 0 | 10 |
| 60 | 5 | 0 | 12 |
| 75 | .... | 0 | 12 |
| 90 | 21 | 14 | 30 |
| 105 | .... | 8 | 28 |
| 120 | 57 | 0 | 18 |
| 135 | .... | 2.7 | 17.7 |
| 150 | 58 | 2.4 | 17.4 |

The patient was readmitted June 3, 1963, about three weeks after discharge, complaining of a continuous cramping pain in the right upper quadrant with occasional vomiting but no hematemesis or melena.

The patient weighed 140 pounds. There was some tenderness in the epigastrium and right subcostal areas. The hemoglobin value and hematocrit at the time of admission were within normal limits and the serum amylase was 120 units. Gastric analysis showed a total 12-hour volume of 1,100 ml and total acidity of 14 units, with free hydrochloric acid zero. A Hollander test was interpreted as positive. After the test was begun, specimens for blood sugar determinations were taken every 30 minutes and gastric aspirations every 15 minutes for two and a half hours. The results are listed in Table 2. An upper gastrointestinal tract roentgen examination revealed no marginal ulcer; however, one was seen on gastroscopy.

At operation June 19, 1963, a posterior marginal ulcer, perforated and walled off, was observed. No intact vagi were found. Total gastrectomy, esophagojejunostomy and end-to-side jejunojejunostomy of Roux-en-y type were carried out. The postoperative course was complicated by infection of the wound and an episode of partial obstruction of the small bowel. At the time this paper was written, the

patient was being examined periodically in the clinic. His general health was good and his body weight was steady at 138 pounds.

## Discussion

In the etiology of the Zollinger-Ellison syndrome the offending cell was originally considered to be the alpha cell in the islets of Langerhans. It was suggested that glucagon, the antagonist to insulin, in overproduction caused the pronounced gastric hypersecretion.[15] It is now known that glucagon depresses both gastric secretions and motility and is not ulcerogenic.[1,4,11] The majority of opinion favors the alpha cell theory. However, since absolute proof is lacking, gamma and delta cells must be considered. Diagnosis of these tumors from microscopic examination is difficult, but electromicroscopic pictures are more convincing of the islet cell origin of the cells.[9]

Gregory and coworkers[3] extracted a potent gastrin-like secretogogue from non-beta islet cell tumors and lesions metastatic from them. It is presently felt that the non-beta islet cell tumor produces gastrin, which stimulates the stomach acid production and ulcerogenesis. Zollinger and Elliott[14] obtained a gastrin-like secretagogue on bioassay of the atrophied pancreas of a patient with hyperplasia and proliferation of islet tissue. A cycle was suggested of chronic calcific pancreatitis with acinar atrophy, islet proliferation and hyperplasia with secretion of a gastrin-like substance, gastric hypersecretion with recurrent ulceration, and acid stimulation of the duodenum to release secretin, which stimulates an already damaged pancreas.[10,14]

Histochemical staining of the gastric mucosa of patients with ulcerogenic tumor revealed hyperplastic changes in the gastric glands which may extend down to include the pylorus. A decided increase in the number of parietal cells was noted.[6,11]

The clinical diagnosis may be confusing. There are many conditions which mimic ulcerogenic tumors; however, the reported cases have not changed the original description of the ulcerogenic syndrome. The onset of symptoms is reported as most common in the fourth and fifth decades of life with a wide range in age at onset. The sex distribution is about equal. The symptoms are related to the high output of acid gastric juice, with the tumor mass rarely the cause of complaint.[12] At present, the large volume of gastric secretion is the only criterion that is more than suggestive of a non-beta islet cell tumor, and the tumor must be suspected when the 12-hour night secretion approaches 2,000 ml, and frequently greater volumes are recorded.[14] The high amount of acid may cause the most characteristic and diagnostic clinical feature of this syndrome—that is, the appearance of a jejunal ulcer just distal to the ligament of Treitz in a patient who has not had gastric operation.

Diarrhea may also be associated with this syndrome. Priest and Alexander,[5] in 1957, noted the significance of an associated enteritis. It occurs in one-third of these patients with ulcer; and in 10 per cent of recorded cases it is the only symptom. In the case herein reported, diarrhea was present and x-ray studies revealed disturbance in the motility pattern. The diarrhea was not intractable. Serum potassium and results of a xylose absorption test were within normal limits. The sprue-like picture did not occur. It may develop due to inactivation of lipase and trypsin from a low pH in the duodenum and jejunum, produced by the large amount of gastric secretions. The mechanism is not clear. The diarrhea may be due to a direct hormonal effect on the small intestine or to irritation of that organ from the large amounts of acid gastric secretion.

The main consideration in the choice of surgical procedure in the present case was difficulty in establishing the pathological diagnosis—that is, no tumor was seen. Zollinger[14] observed in 132 collected cases of such tumors that 62 per cent were malignant. Also, 40 per cent had metastatic lesions which produced the gastric secretagogue. With 26 per cent of the tumors multiple throughout the pancreas, there are multiple sites for the potential gastric secretagogue in 55 per cent of the cases. He pointed out that the recurrence rate of ulceration following local removal of tumor and radical gastric resection combined with partial removal of the pancreas was about 60 per cent. It was nil following total gastrectomy. Yet the mortality was about the same with all three approaches—about 15 per cent. Therefore, the best protection against recurrent difficulty is total gastrectomy with resection of obvious tumors, especially when located in the tail and body of the pancreas. As with the case reported here, when the clinical history is very suggestive of an ulcerogenic tumor but none is found at operation, resection of the body and tail of the pancreas should be considered. This may establish the presence of either small and diffuse involvement of the islets or hyperplasia.[13,16]

When recurrent ulcerations develop (which was the situation in the present case at its second admission) despite a previous radical gastric resection, total gastrectomy should be considered. However, in a patient who has had no previous operation, with as positive a clinical diagnosis of Zollinger-Ellison syndrome as the case reported here, are we justified in doing a total gastrectomy without pathological diagnosis?

It is unusual for the surgeon to see ulcerogenic tumor except in those cases of severe ulcer disease

which cannot be controlled by any of the current surgical procedures. Certainly, early recurrent ulceration with pronounced gastric hypersecretion, despite vagotomy and a radical gastric resection, is very suggestive of the Zollinger-Ellison syndrome. Three weeks after discharge, the patient in the present case returned with recurrent ulceration and hypersecretion but a positive Hollander test.

There are other causes of operative failure which imitate ulcerogenic tumors and are far more common. These include incomplete vagotomy and any procedure that interferes with drainage of the antrum.

It must be remembered that recurrent ulcerations may result from ingestion of drugs—for example, cortisone, salicylates or reserpine. More commonly a patient may stimulate gastric secretions by ingestion of alcohol or such caffeine-containing drinks as coffee, tea and cola. Ulcerogenic tumors account for a very small proportion of medical and surgical failures.[13]

Although incomplete vagotomy and possibly alcoholic intake were thought to be factors in the present case, the patient also returned early with an appearance of recurrent ulcer and hypersecretion. With a pathological diagnosis of islet cell hyperplasia and a clinical diagnosis of Zollinger-Ellison syndrome, total gastrectomy would be the procedure of choice.

Irradiation treatment to the remaining stomach to control secretions has been generally unsuccessful. However, the possibility of avoiding total gastrectomy with a combination of radioactive isotopes ($P^{32}$), chemotherapy and irradiation has been suggested for certain cases in which there were metastatic ulcerogenic tumors.[8]

## Summary

A case clinically compatible with the Zollinger-Ellison syndrome with pancreatic islet cell hyperplasia is reported. The pertinent literature is reviewed and the surgical management is discussed.

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# GLAUCOMA Secondary to Local Steroid Therapy

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WITH THE WIDESPREAD USE of local steroid therapy for a number of ocular conditions, complications secondary to the treatment have become evident. In recent years, the increasing incidence of serious complications of herpes simplex of the cornea has been laid to activation or stimulation of the virus by steroids.

Recently it has been reported that glaucoma may be a complication of the local use of steroids in the eye.[4] Reports have noted increase in ocular tension

Submitted January 7, 1964.